Meeting of the
Pharmacy and Therapeutics Committee
September 3, 2003
Minutes

Members Present:
Randy Axelrod, M.D., Chair
Gill Abernathy, R.Ph.
Eleanor S. (Sue) Cantrell, M.D.
Avtar Dhillon, M.D.
Mariann Johnson, M.D.
Mark Oley, R.Ph.
James Reinhard. M.D.
Mark Szalwinski, R.Ph Vice Chair
Christine Tully, M.D.
Renita Warren, PharmD

Arthur Garson, Jr. (via phone), M.D.

Absent:
Roy Beveridge, M.D.

A quorum was present

Guests:
Jane Woods, Secretary of Health and Human Resources
66 representatives from pharmaceutical companies, providers, advocates, associations, etc.
Manikoth Kurup, MD, Member, Board of Medical Assistance Services

DMAS Staff:
Patrick Finnerty, Agency Director
Cynthia Jones, Chief Deputy Director
Paige Fitzgerald, Counsel to the Board, Office of the Attorney General
Bryan Tomlinson, Director, Division Health Care Services
Adrienne Fegans, Program Operations Administrator
David Shepherd, Pharmacist

Absent:
Cheryl Roberts, Deputy Director of Programs and Operations

First Health Staff:
Donna Johnson, Pharmacist, VA Clinical Account Manager
David Adams, PharmD, Rebate Support
Carol Perkins, PharmD, Clinical Support
Marianne R. Rollings, Pharmacist, Education Specialist
Sandra Kapur, Clinical Pharmacist

WELCOME AND INTRODUCTIONS

Upon arrival of committee members sufficient to form a quorum, Chairman Axelrod called the meeting to order. It is noted that 1 member was in attendance via telephone, but he was not included in the count toward a quorum nor did he vote.

The chairman welcomed those in attendance and commented that there was a lot of work to be done. He indicated that a short review of the previously presented drug classes would be done prior to voting on them. Voting did not occur at the previous meeting, due to lack of a quorum. New classes on today's agenda would then be addressed.

Prior to receiving the minutes of the previous meetings, Dr. Axelrod introduced Virginia's Secretary of Health and Human Resources, the Honorable Jane Woods.

COMMENTS FROM THE SECRETARY OF HEALTH AND HUMAN RESOURCES

The Honorable Jane Woods, Secretary of Health and Human Resources brought greeting to all involved in the process and announced that at this juncture it would be appropriate to reiterate the commitment and assurances related to this initiative. She stated that she believes this process and product can and must work for Virginians. It will be accomplished not by importing another state's product, but by being designed specifically for Virginia. It must be usable and user friendly.

Secretary Woods expressed her appreciation for the input and cooperation at the numerous meetings related to this initiative. She mentioned the contributions of many interested parties. The Virginia process has been noted for being different from those of other states. The Secretary commented on the incredible pool of talent represented by the P&T Committee and extended her thanks for the dedication and time commitment of the committee. The Secretary noted that this group has been extended broad latitude to make this program work for Virginia.

It was duly noted that the contractor for this initiative is First Health Services Corporation (FHSC), a Virginia-based company. The role of FHSC has been defined as the designated entity to provide operational and mechanical support and expertise to the implementation of the Preferred Drug List (PDL) program for Virginia. She noted that FHSC will provide support for the decisions made by the P&T Committee.

A PDL Implementation Advisory panel has been designated to provide input from shareholders in the process. They will be instrumental in helping to educate and assist their constituencies. That group is scheduled to meet on September 11th.

Secretary Woods announced that she would like to share with those present the key decision that has been made regarding an important component of the PDL program. Virginia has determined not to be a participant in the multi-state "pooled rebate" program. The Virginia program will be based on a stand-alone system of supplemental rebates. She noted that there are easier ways to do this portion of the program, but that this is a program for Virginia. FHSC will be negotiating the supplemental rebates on behalf of DMAS. The process for implementation of Virginia-specific rebates is to be posted on the Department of Medical Assistance Services (DMAS) website www.dmas.state.va.us on September 4th. The process is on a very fast track, as required by the General Assembly.

A template for rebate participation and pricing information will be available to all potential participants. Packets, including copies of the template, will be sent to known prospective rebate participants. Classes reviewed in P&T Committee meetings in July, August and September will be implemented beginning January 2004. Best and final pricing offers are due by Friday, October 3rd. The P&T Committee will meet on October 15th to make the decision as to which products will be prior authorized and which will be excluded. November 7th is the date for final contract execution. Secretary Woods indicated that the participants in this effort are expected to benefit from their previous history of such submissions to other states' programs. The process is doable and she has received assurances that the companies will cooperate in this endeavor. During the week of November 11th, the P&T Committee then will review the classes of drugs to be included in the April 4th implementation process and will make any necessary adjustments to the first PDL implementation.

The Secretary closed by reiterating the importance of this initiative to all Virginians. It is a lifeline to citizens who depend on DMAS. She said Virginia will be credited with developing a program second to none.

ACCEPTANCE OF MINUTES FROM JULY 30TH AND AUGUST 12TH MEETINGS

Dr. Axelrod noted a correction to the minutes of the August 12th had been presented by Dr. Zuckerman regarding the Lipitor presentation. He stated that the decrease in LDL noted was 61% and there were no obvious adverse clinical effects, including myopathies.

Upon request of the Chairman, the Committee voted on a motion and second (Szalwinski/Johnson) to receive the minutes of the July 30th meeting. The Committee voted unanimously to receive the minutes as presented.

Upon request of the Chairman, the Committee voted on a motion and second (Szalwinski/Johnson) to receive the corrected minutes of the August 12th meeting. The Committee voted unanimously to receive the minutes as corrected.

COMMENTS FROM THE CHAIRPERSON

Dr. Axelrod reminded the members that they had received a letter from Patrick Finnerty, DMAS Director, regarding confidentiality requirements of membership on the P&T Committee. Since Committee members will be reviewing confidential drug pricing information as part of their duties, Dr Axelrod reminded them to review the letter from Mr. Finnerty. Reference was made to Code Section 2.2-3103, which prohibits certain conduct by those having and knowing information related to their position as an appointee. Special reference was made to sub-paragraph 4 of the statute, regarding use of confidential information from the activities of the Committee for a member's own economic benefit or that of another party.

Dr. Axelrod reiterated that this program is based on integrity, both personal and professional, and that the Committee should be dedicated to that concept in all deliberations.

It was noted that 20 presenters would be speaking. Time constraints were noted. Presenters would have 3 minutes, and were expected to begin a summary of remarks at 2½ minutes. A time clock would be visible to speakers and an amber light would flash at 2½ min., then a red light at 3 minutes. The Chairman thanked the clinical staff from FHSC for the extensive amount of evidence-based background materials made available for review by the Committee in preparation for the meeting.

DRUG CLASS DISCUSSIONS

- **FOLLOW UP OF DRUG CLASSES REVIEWED ON 8/12/03**

Since there was not a quorum at the August 12th meeting, voting on the classes presented at that meeting did not occur. In preparation for a vote on those classes, the Committee has received additional requests to speak to issues with 2 of the classes before the Committee votes.

1. SELECTIVE COX-2 INHIBITORS

The first additional presenter was **Maureen Corson**, PharmD, a medical research specialist from Pfizer, speaking about studies involving Celebrex and Bextra. She spoke about cardio/renal safety and GI safety. Cardio/renal safety – due to concomitant hypertension in many patients with osteo- or rheumatoid arthritis, the CRAFT Study was used to document labeling. It involved over 8000

patients for a period of approx. 9 months. As a result of this study, the Celebrex label is not required to contain information regarding caution in ischemic heart disease.

OPERA -The second study involved patients greater than 65 years of age who have hypertension and osteoarthritis. Compared to Vioxx, Celebrex showed reduced incidence of edema and destabilization.

Related to GI safety of Celebrex vs. Bextra, studies at 8 times the normal OA/RA dose showed reduction in complications in comparison to traditional NSAIDs.

3 leading arthritis and pain guidelines support the use of COX-2 inhibitors:
American Pain Society Guidelines
American College of Rheumatology Guidelines
American Geriatric Society Guidelines

Dr. Axelrod noted the variance in designation of pain in the different models: In ATF the pain designators were "mild" and "moderate to severe", while the APR study encompassed all 3 levels "mild to moderate" or "mild to severe". He mentioned the appropriate use of APAP in the regimen of these patients as noted in ATF. In response: Different models for studies were used. ATF was looking at short-term pain management of acute pain, whereas OA/RA was long-term use. These were differentiated out due to mediators.

The second presenter was **Laurie Cooksey**, PharmD, a Clinical Pain Specialist at VCU/MCV.

Ms. Cooksey noted the JCAHO requirement that appropriate pain management be available to patients. She cited the need for access to the tools to provide such results.

Ms. Cooksey reiterated the 4 pain pathways: transduction, transmission, perception, and modulation. Transduction, the first step, involves prostaglandins. This is the ideal place to dampen pain. The COX enzymes are involved. COX-1 enzymes is the "housekeeping" enzyme, present all the time – helping with stomach, kidneys, etc. Cox-2 enzyme is "inducible", specifically for inflammation. Since attacking Cox-1 has broad implications, COX-2 therapy is preferable. Certain types of pain are especially responsive to prostaglandin inhibitors (cf. bone pain, OB/GYN pain). They are post-synaptically mediated. Opiates do not treat this type pain well, they only mask it. Cancer and OB pain respond well to COX-2's.

Ms. Cooksey referenced studies of aspirin vs. traditional NSAID therapy and the potential adverse effects of combining the two products. Studies have shown that chronic use of traditional NSAID therapy in conjunction with aspirin, where the aspirin is used prophylactically for patients at risk of MI, creates a situation that negates the aspirin's cardio-protective effect. The risk of MI is increased 2-fold.

There are 3 COX-2 products on the market. MCV formulary has only Celebrex, with some availability of Bextra. Ms Cooksey admits that she brings a certain bias, since MCV does not include Vioxx on its formulary as a result of certain negative aspects of its therapeutic profile.

Ms. Cooksey reiterated the need for COX-2 therapy to be available to fulfill the charge of the Joint Commission. Dr. Axelrod inquired as to whether this presenter or her division is the recipient of any grants from pharmaceutical organizations. She responded "No."

The chairman reminded the Committee that previously submitted comments on this class would be considered in the deliberations if this class is determined PDL – eligible. The Committee was asked if the COX-2 therapeutic class should be considered eligible for inclusion in the PDL. Upon motion and second (Szalwinski/Oley) to include this class, the question was voted upon and passed unanimously. Tim Garson, present via phone, asked for clarification of his ability to vote. The chairman stated that only members physically present could cast a vote. Dr. Garson, therefore, did not vote on any questions at the meeting.

2. HMG-CoA REDUCTASE INHIBITORS

An additional speaker, **Dr. David Booze**, addressed comments for the class of "statin" drugs. He noted that the LDL-lowering product he wanted to present (Crestor) had been approved at 4:52 P.M. on the very day of the last meeting. As such he was unable to speak to the merits of Crestor.

Dr. Booze noted that coronary heart disease is the leading cause of cardiovascular morbidity and mortality in the country. The NCEPATT-3 Guidelines have determined that LDL cholesterol is the primary risk factor for lowering cardiovascular events. New guidelines stress much more aggressive lowering of the LDL cholesterol, increasing the pool of patient candidates for drug therapy to nearly 40 million. Twenty million of those patients have a total LDL goal of less than 100. The more aggressive goals need more effective therapy. Dr. Booze offered that Crestor should be considered for that role.

Dr. Booze stated this product has been involved in a number of studies of hypercholesterolemic patients. He referenced the largest trial, the STELLAR study, published in the American Journal of Cardiology. This was a comparative trial of over 2200 patients. Crestor in a dosage range of 10 to 40 mg was compared to the full dosage range of atorvastatin, simvastatin, and pravastatin. The results show that there was a 35-50% LDL lowering with the 10 mg dose. Reduction of LDL exceeded the full dose of Pravachol, the full dosage range of Zocor except for the 80 mg strength, and is consistent with 20 to 40 mg of Lipitor. There was a consistent increase of HDL across the dosage range, which is numerically and statistically superior to other agents in the class, between 8-12%.

Relative to achievement of NCEPATT-3 treatment goals, Dr. Booze stated that at starting dose there is approximately 80-85% improvement on the first pass, obviating the need for titration.

Upon a question from the panel, Dr. Booze noted that doses studied were 1 to 80 mg. Since there was no improved risk/benefit ratio beyond 40 mg, the 80 mg dose was not included in the product line. Approved dose is 5 to 40 mg in the US. The normal starting dose is 10 mg, with a 5 mg starting dose for patients on cyclosporine or genfibrozil therapy, or those with severe renal impairment.

Joanne Trainer, PharmD, from the cardiovascular division of Pfizer, presented additional information re: atorvastatin's safety, efficacy and outcomes trials. .

She noted an efficacy of up to 61%, excellent safety profile across 10-80 mg dose range. The historic number of patients on atorvastatin therapy is noted at 88,000 or 48 million patient-years of experience. She cited the fact that recent trials have been stopped due to the evident improved benefit of atorvastatin use. The product does not interact with warfarin or protease inhibitors. No

record of significant interaction when used with amlodipine or verapamil. Recent studies show lack of interaction with Plavix. There were no questions.

Dr. Axelrod took a moment to commend the presenters on maintaining the time constraints of the meeting.

The chairman then asked for the Committee's decision on whether to include the HMG-CoA Reductase Inhibitors ("statins") as eligible for inclusion in a PDL. By motion and second (Oley/Johnson) the question was presented and approved unanimously by the members attending. No vote was submitted via phone.

3. SEDATIVE HYPNOTICS

No additional presenters. Motion and second (Tully/Cantrell) moved the question. The vote was unanimous to include this therapeutic class in the PDL. No vote was submitted via phone.

4. BETA ADRENERGICS

No additional presenters. Motion and second (Szalwinski/Cantrell) moved the question. The vote was unanimous to include this therapeutic class in the PDL. No vote was submitted via phone.

5. INHALED CORTICOSTEROIDS

No additional presenters. Motion and second (Tully/Szalwinski) moved the question. The vote was unanimous to include this therapeutic class in the PDL. No vote was submitted via phone.

- **PRESENTATIONS ON NEW DRUG-SPECIFIC CLINICAL INFORMATION**

1. ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)

The first presenter was **Christine Dubé**, PharmD, Sr. Regional Clinical Manager, Abbott. She provided information on the product, Mavik (trandolapril) an ACEI. Ms. Dubé cited several studies to stress the special qualities of these products.

Mortality/Morbidity data
Mavik was the focal drug in the TRACE study and was shown to reduce all-cause mortality by 22%. Specifically, cardiovascular mortality (25% risk reduction), sudden death (24% risk reduction), and progression to severe CHF in patients with reduced left ventricular function soon after MI (29% risk reduction). The NIH has chosen Mavik to be the ACEI in the PEACE trials evaluating the protective effects of this class in relation to conventional therapy.

Favorable pharmacokinetic/pharmacodynamic profile
True once-daily drug. High lipophilicity, improves transport into organs with high ACE concentrations, such as the heart and kidney. Excretion through both liver and kidney expands use in at-risk populations. The peak to trough ratio is high (an increase of 50%), allowing sustained BP control over a full 24 hr.

Only ACE with an African-American dosing indication
Product is competitively priced as to other ACEIs, and even to generics on market.

Jerry Brown of Solvay presented information on Aceon – As a prelude, he noted the American Heart Association estimated the cost of $47.2 billion for direct and indirect costs of hypertensive disease in 2002. He gave a figure from JNC-7 of 34% for patients controlled with antihypertensive therapy, or 13 million patients (defined by the American Heart Association).

The ACT trial was developed to provide an analysis of the effectiveness of Aceon in the community. It was a multi-site study comprised of over 8000 patients in the community setting. Mr. Brown stated that clinical trials do not accurately reflect the effectiveness of a product in the general population practice setting. Aceon was used at a dose of 4 to 8 mg as monotherapy in a hypertensive patient population with participants from the following groups: newly diagnosed, those with inability to tolerate other therapies or those who had failed to respond to other products as monotherapy. After 12 weeks c. 37.2% of patients were found to have a BP of less than 140/90. The average decrease in systolic pressure was 17.5mm Hg and diastolic decreased an average of 10.7 mm Hg. In 34.5% of the cases, patients responded to Aceon who had been unresponsive to other ACEIs. Duration of therapy on other ACEI products ranged from 7.6 to 36.9 months.

Unique FDA-approved labeling of Aceon states that in patients with essential hypertension there is a reduction in BP and reduction in peripheral resistance without a significant change in heart rate or BFR.

After this presentation, Dr. Axelrod commented that the 34% treatment success rate for hypertension is remarkable and also unacceptable. He noted that considerable education of the medical community is necessary in regard to this statistic.

Robert Garris of Wyeth Global Medical Affairs presented remarks about the product, Altace.

Mr. Garris stated that ACEIs are highly effective and underutilized in the treatment of hypertension, heart failure and MI, as well as renal disease prevention. He highlighted the HOPE study in his remarks. The HOPE study was a randomized trial with Altace and placebo. The population of 9300 patients studied was 55 and older, at high risk for cardiovascular events. Patients were randomized on Altace and placebo with dose titrated up to 10 mg from placebo. Improvement was noted quickly within 1 yr. and sustained over the 4½ yr. of the trial. The results were a 22% reduction in MI, stroke and cardiovascular death; with a 32% decrease overall in stroke and a 61% decrease in fatal stroke. He stated there was also a significant reduction in functional and cognitive impairment shown in the data.

Secondary outcomes noted were significant cost reduction in cardiovascular procedures, diabetes complications, and prevention of heart failure. Significant new findings indicate a decrease in new-onset diabetes. The last is being followed up on currently. Women and elderly receive the same benefits as the general population. Data regarding c. 3600 diabetic patients also showed equivalent results. As a result the ADA 2003 guidelines now show that affected individuals 55 and older should be protected with ACEI. Altace is only agent approved for the indication of cardiovascular risk reduction.

Mr. Garris noted the capsule formulation of Altace in unique in the class and allows for flexible dosing options in patients unable to use tablet formulations.

There were no additional presenters.

Summary –ACEIs - Mark Oley

Mark Oley provided a summary presentation on the ACEI class.

The mechanism of action for these drugs is suppression of the renal angiotensin aldosterone systems. They prevent conversion of angiotensin I to angiotensin II, a potent endogenous vasoconstrictor. There are 10 products available in the class, with 4 currently available as generic products and 2 of the products pending change to generic availability. Almost all have combinations available, with the bulk of combination products being combined with hydrochlorothiazide.

While American Diabetes Association 2002 guidelines recommend ARBs as the agent of choice in diabetic patients showing clinical signs of nephropathy, ACEIs are considered first line therapy in Diabetes-I patients. ACEIs are recommended as first-line agents in patients with heart failure and in those who have had MI with systolic dysfunction. In cardiac patients with heart failure, the choice of enalopril as the first-line agent can be extrapolated to others in the therapeutic class. No trials have shown tissue ACE inhibitors are superior. It may be prudent to limit selected products, however, to those that have clinical trial data available. If target doses cannot be used, a decreased dose may be attempted.

The HOPE trial was confined to 1 agent with high binding affinity. The high tissue bonding affinity of Altace may have been responsible for the success of the study. It was noted that the HOPE trial was not a comparison of agents, but a trial of product efficacy vs. placebo. Other products in the class are placed in a hierarchy of binding as follows: Accupril and Lotensin, greater than Altace; which is greater than Aceon. Following those products are Prinivil/Zestril, then Vasotec, then Monopril, then Capoten.

Mr. Oley recommended that the Therapeutic Class of ACE Inhibitors be made PDL eligible.

Dr. Tully asked if there was a difference in response between the Caucasian and African-American populations related to this therapeutic class. Mr. Oley responded there is evidence to support better response in the African-American population with Mavik. Upon request for additional information if available, Ms. Dubé responded that requests had been made twice for adding that to the labels of enalopril and lisinopril, but not approved. Mr. Garris indicated there were some publications related to Altace, but he was not familiar with whether the information had been submitted.

Dr. Axelrod asked if the Committee was ready to vote. Motion and second (Abernathy/Tully) moved the question. The vote was unanimous to include this therapeutic class in the PDL. No vote was submitted via phone.

Dr. Reinhard asked for clarification of the vote, as to whether this was for the class or the individual products presented. Dr. Axelrod responded that at this point, the class is being considered. Specific products are not restricted by this action.

2. ANGIOTENSIN II RECEPTOR ANTAGONISTS (ARB)

Kathy Campbell, PharmD, Bristol-Myers Squibb/ Sanofi Synthlabo provided information on Arbasartan, a second generation ARB. Ms. Campbell noted the product's improved pharmacokinetic and pharmacodynamic profiles. The product has a half-life of 11 to 15 hours, with 80% bioavailability. She noted a 60% improvement in mild to moderate at 300 mg

Ambulatory blood pressure monitoring data showed no improved effects with the use of a divided dose. Diabetes nephropathy – New England Journal of Medicine 2001 cited the PRIME study where a 300 mg dose provided a 70% risk reduction with microproteinuria. IDNT with losartan progressed to ESRD.

This product has approved indications for diabetic nephropathy and hypertension. The ADA recommendation is for use of this product as first-line therapy for patients with diabetes and proteinuria.

James Rowenhorst, Boerhinger-Ingelheim, presented information on Micardis and Micardis HCT. He noted the critical advantage of this ARB in patient compliance, 24 hr BP control, and ability to regulate hypertension. The therapeutic advantage of ARBs over ACEI products is the absence of ACEI-induced cough, as well as once daily dosing. Control is maintained even during the early morning hours and its effect is superior in the last 4 to 6 hr of the 24-hour cycle. This product is effective in a racially diverse population and in its combination form; the product is twice as effective as the individual components when dosed alone.

Ray Lancaster, PharmD**,** Novartis Pharmaceuticals, requested inclusion of Diovan in any considerations of this class. He noted action similar to calcium channel blockers, beta blockers and ACEIs. He noted the variances in trials of antihypertensive products. Sixteen placebo and controlled trials were used as examples. Mr. Lancaster noted that Diovan is the only product with an indication for heart failure. The budget impact of using this product can be shown in decreased hospitalizations and related costs.

Dr. Kerry Edwards, Regional Medical Director, Merck, presented Cozaar. He noted the evidence-based data available related to heart outcomes studies. Dr. Edwards noted the nephroprotecive effects of the ACEI class. In the LIFE study of more than 9000 patients, strokes were decreased by 25%. Additional reductions in MI and other cardiovascular events were noted. In patients with DMII, end stage renal disease was decreased by 16%. Saving over 3.5 years for 100 patients showed a decrease in ESRD of 6.3, thereby decreasing hospital days by 1/3.

Dr. David Booze addressed the Committee on the issue of Atacand, a once-daily ARB with a high trough to peak ratio. It has a comparable loading dose to amlodipine. He gave a figure of 90 to 100 % efficacy and mentioned its inclusion in the CHARM study, which was reported at the European Society of Cardiology within the week. The product has a 48 to 72 hour efficacy. It is effective in reducing systolic pressure in patients intolerant to ACEI products. As add-on therapy to ACEIs, beta blockers and loop diuretics the product has the advantage of not being affected by CP450 metabolism. It reduced hospitalizations from heart failure by 20 %.

There were no additional presenters.

Summary of the ARB Class – Mark Oley

Mr. Oley noted the mechanism of action of this class, which also affects the renin-angiotensin aldosterone system. The ARBs block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, notably vascular smooth muscle and the adrenal gland.

There are currently 7 products in this class on the market, all brand-only; all can be had in combination with hydrochlorothiazide. It was noted that combination with a low-dose diuretic creates a synergism. While it has been hypothesized that ARBs differ in the way they block AT1, it is probable that all exhibit surmontable (competitive) binding. There is no evidence of clinical differences when ARBs are used in therapeutic doses. All are structurally related to losartan except for Teveten.

The ADA recommends products from this class for DM-II diabetic nephropathy and hypertension as initial therapy. ACEIs are still the drug of choice in DM-I hypertensive and non-hypertensive patients. No dose adjustment is necessary in the elderly over the youth population. The products are effective to a lesser degree for hypertension in African-Americans than Caucasians.

Mr. Oley recommended that this class be included as PDL eligible.

Ms. Warren raised the question as to whether the combination products are included in PDL considerations. It was noted that they are included and may present some cost savings over use of the components individually. A request for clarification of patent status elicited the response that Diovan (1996) and Cozaar (1995) would be the first candidates for generic products.

It was asked how the African-American population will be handled for this class. Dr. Axelrod responded that a reasonable clinical approach is anticipated and mentioned step therapy as well as evidence based protocols, which will address any special populations. He mentioned the use of the medical schools (UVA, MCV and EVMS) as possible resources for such step therapy and protocol development.

Dr. Axelrod asked if the Committee was ready to vote. Motion and second (Szalwinski/Tully) moved the question. The vote was unanimous to include this therapeutic class in the PDL. No vote was submitted via phone.

BREAK

3. CALCIUM CHANNEL BLOCKERS (CCBs)

Joann Trainer, Pfizer, presented on the CCB Norvasc (amlodipine). She noted that it can be used safely and shows cardiovascular benefit. It is the most widely used CCB and has been studied for its pharmacokinetic profile. She cited a Veterans' Administration multicenter trial called ALLHAT, underwritten by NIH. This was the first study with CCB to define morbidity and mortality outcomes. It addressed the comparative effects of chlorthalidone, amlodipine and lisinopril on combined fatal coronary heart disease and non-fatal MI. This was a retroactive study in which the specific population was prespecified. The effect of amlodipine was comparable to chlorthalidone and similar in the Black population. There was less angioedema. There was less need for K+ supplementation. The product was accepted for use in decreasing BP in newly

diagnosed DM-II patients with cardio problems; it decreased BP across all types of diabetics. The pharmacoeconomic profile is favorable at a cost of 52% of most monotherapy.

Dr. Axelrod referenced the ALLHAT study of 40,000 patients and its value equation. He stated the need for good endpoints and savings. It was noted that pennies a day can save dollars a day. He noted sometimes it is necessary to use 3 or 4 meds to get to goal. He asked if there is mortality data on CCBs being better therapy than other choices. The answer was no.

The presenter noted the importance of the expansion of studies for the fragile elderly and African-Americans. She reiterated that 3 or 4 drugs may be needed, not just an added diuretic.

Christine Dubé returned to speak regarding the combination product, Tarka. It is a combination of the CCB verapamil and Trendal, effective in decreasing proteinuria. The drug profile shows reduction of markers for cardiovascular problems, strokes and CAD. She noted new BP goals are decreased to 130/80 and that in patients with proteinuria the goal is 125/75. This product is included in the National Kidney Foundation and JNC guidelines. It is metabolically neutral to sugar, lipids, etc. and Ms. Dubé stated that the combination improves persistency by patients. Ms. Warren asked if there have been studies targeting African-American population. Ms. Dubé stated such low renal secretion patients sometimes do not respond to diuretics.

Dr. J. V. Nixon, professor of Medicine and Cardiology at MCV/VCU spoke to the necessity of including amlodipine in any PDL considerations. He cited its indications for both hypertension and angina and noted it is the only product in this class used for both conditions. It is especially effective in hypertension and well documented for reaching target levels, while being effective in subgroups. It is more effective in females than males and equal in African-Americans vs. Caucasians. Efficacy is similar in populations over 65 years of age to that in those under 65 years.

Dr. Nixon cited the ALLHAT study with a broad-based study cohort: 47% female, 36% diabetic, 35% African-American. Approximately 32,000 patients completed the study. The age limit was 55+ and 63% of the patients required 2 or more drugs. This was the largest trial ever of antihypertensives in a population of mild to moderately hypertensive patients. It was a controlled study population without renal disease.

Dr. Nixon stated the product has been on the MCV formulary since 1992 and has 2 years before the patent expires. He urged the product be included as a preferred drug.

Kimberly Thornton, Reliant Pharmaceuticals, presented Dynacirc CR for consideration. She noted it is a product safe and effective for use in hypertension regardless of age, race or gender. It is effective in doses of 5, 10 and 15 mg to decrease both diastolic and systolic pressure. In a comparison of the 5 and 10 mg doses, there was a head-to-head trial of this product vs. Plendil where Plendil was d/c'd for six weeks and Dynacirc CR exchanged for it. Then the pt. was returned to Plendil. In the 10 mg dose, there was a significant difference of 61% to 87% improvement with Dynacirc CR. Plendil also showed greater incidence of pedal edema, as did Norvasc.

Carmita Coleman, PharmD, assistant Professor of Pharmacy Practice, Hampton University School of Pharmacy, addressed the Committee. She spoke to the importance of considering ethnicity in the Committee's deliberations. She spoke to a consensus statement relating to African-American patients at-risk. African-American children are especially vulnerable. Females,

as early as 10 years, are at higher risk for hypertension vs. Caucasians. Reference was made to the ALLHAT study which included 35% African-Americans. Also noted was JNC-7, which showed it generally took 2 or more antihypertensive products to reach goal. Therefore, combination therapy is considered first-line in the African American population. Amlodipine provided significantly lower diastolic levels than other products. Again she noted monotherapy is not the regimen of choice for this population.

Dr. Axelrod thanked the presenter and asked for disclosure of any grants that this presenter or her university might have received from the pharmaceutical industry. Ms. Coleman stated she has received none and that the School of Pharmacy grants are all from the government.

Mr. Szalwinski asked if the presenter had any "bullets" to present. Ms. Coleman stated the following: Amlodipine shows a relatively good profile without significant downside (except the grapefruit interaction). It can be used for hypertension, angina and vasospastic angina. Her second offer of information was that once-daily dosing is preferable in order to increase adherence..

Dr. Axelrod asked "outside the formulary" what policy should be embraced to improve the health status of the African-American population. The response was that healthcare providers need to be educated, preferably as a team including physicians, pharmacists and nurses. She noted the silent killer, hypertension, in the Medicaid population and stated patients need to be educated and aware of their target levels.

No additional presenters were heard.

Summary of Calcium Channel Blockers – Mark Szalwinski

Dihydropyridine Type

Mr. Szalwinski referred the Committee to the extensive handout on the topic. Of the 7 products available in this category, he noted 6 are indicated only for hypertension and/or angina. The exception is amlodipine, which has 3 indications including cerebral arteries and SAH. He noted the use of verapamil and diltiazem for long-term therapy. These products are available in multiple dosage forms.

Non-Dihydropyridine Type

Mr. Szalwinski referred the Committee to citations related to specific indications for nifetipine (hypertension), Dynacirc (hypertension only), Nicardipine – (angina and hypertension).

Norvasc is used for the 3 indications noted in the previous presentations. It has a long half-life. Plendil is used for hypertension. All have a similar safety and efficacy profile, with marginal differences, except nizatapine. That product is greater for SAH.

Unique short-acting products were mentioned and cautions were stated to be available in the PRAISE and PRAISE-II studies.

Vasocor is a unique product with fast influx. Its only indication is angina. Diltiazem is indicated for both kinds of angina and for hypertension. Mention was made of the use of verapamil in

chronotherapy by dosing at bedtime. The original product is available in a large number of generic formulations. Indications are for angina, arrhythmias and hypertension.

Mr. Szalwinski recommended inclusion of this class in the PDL.

Dr. Axelrod asked if the Committee was ready to vote. Motion and second (Oley/Johnson) moved the question. The vote was unanimous to include this therapeutic class in the PDL. No vote was submitted via phone.

4. BETA ADRENERGIC BLOCKING AGENTS

Kerry Cunningham, PharmD**,** GlaxoSmithKline, Regional Medical Scientist, presented information on Coreg. This is the only beta-blocker approved for a full range of therapies, including heart failure. She referenced the NYHA Stage IV study, COPERNICUS, which showed a 34% decrease in all cause mortality with this product. Also noted was the COMET study, which compared metoprolol (Beta-1 selective) vs. Coreg (non-selective and alpha blocker) therapy. The July "Lancet" shows a 17% decrease in all-cause mortality with Coreg. A decrease of 20% in cardiovascular mortality was noted and 67% decrease in strokes, as well as a 22% risk decrease on the onset of diabetes. In several studies there were reduced hospitalizations and lower costs with Coreg at a medical cost savings of approximately $6000/patient.

Ms. Abernathy requested information on the difference of dosing with metaprolol tartrate. In response it was noted that in equivalent doses there was equivalent beta-1 reduction.

Kimberly Thornton, Reliant Pharmaceuticals, returned to address the issue of propranolol HCl, a non-selective beta blocker for hypertension. Her company has reformulated the 80 and 120 mg dose into capsules designed for bedtime dosing. This is to potentiate a means of affecting changes during circadian cycles. Delayed release of therapy is anticipated to create the reduction of incidence of stroke, congestive heart failure, cardiac death and sudden death. It is also controlled release.

In the BHAT trials, which were multicenter and randomized, study participants had at least 1 MI and received beta blockers. There was a reduction in mortality of 26% with propranolol vs. placebo. The decrease in mortality in early morning hours is notable.

Dr. David Booze, presented information on Toprol-XL, metoprolol tartrate. He stated this is the only beta blocker with indications for hypertension, angina and congestive heart failure. He addressed the issue of pharmacokinetics and pharmacodynamics, citing a 4 hr half-life of metoprolol and 3 to 4 times daily regimen. In the COMET study, dosing is twice daily. The COMET study should be noted for under-dosing. The MERIT HF and COPERNICUS studies were also mentioned and the populations were noted as different, but results were virtually superimposable.

Dr. Axelrod questioned the status of any ANDA for this product that was filed in April, but received no response. Ms. Abernathy asked about Stage IV, but was told that it was only a subset of the study, MERIT HF, which was cited.

Dr. Phillip Duncan, Virginia Heart Group, was the final presenter. Dr. Duncan is a cardiologist.

Dr. Axelrod asked if there was any potential conflict with this presentation and Dr. Duncan's allegiance to any manufacturer. Dr. Duncan stated that although he has been part of a speakers' bureau, his presentation to the Committee was being done on behalf of his patients and there was no conflict.

Dr. Duncan noted that carbetolol had proved especially useful to him because it is indicated for heart failure. He presented a chart of various studies. He cited the BEST study that showed negative results in African-Americans. Carbetolol has proved useful because of its pan activity on B1, B2, A1 differences and its significant antioxidant effect. Dr. Duncan spoke to the prospective inclusion of African-American use of carbetolol in the carbetolol trial. It was a significant subgroup analysis. COPERNICUS was an important event. He noted the dosing schedule in heart failure. Only 2 classes of drugs have been used effectively for heart failure. ACEI and beta blockers are dosed for heart failure prevention, with 55% of patients receiving beta blockers post hospitalization.

When asked for help in improving outcomes, Dr. Duncan expressed a need to educate practitioners about cardiac care. Many studies have been done which show good results before guidelines are established. He noted pharmacists could be helpful in sharing information.

Dr. Axelrod asked if Dr. Duncan used a step approach in his care plans for heart failure. Dr. Duncan concurred, stating he felt there was currently over-aggressive use of diuretic therapy. He stated there is an underutilization of beta blockers. Dr. Axelrod asked if this presenter has a choice product in the ACE category. Dr. Duncan responded that he likes Altace post-HOPE. He also uses generic lisinopril and has tried others. He uses whatever is appropriate.

There were no other presenters.

Summary of Beta Adrenergic Blocking Agents (Beta Blockers) – Mark Szalwinski

Mr. Szalwinski again referred the Committee to the extensive background document. He noted that most of the products in this therapeutic class have generic versions available. That includes the non-selective as well as the B1 selective and the B1, B2 selective products. He noted difference in the product, Coreg, related to CHF.

In reviewing the class, Trandate was mentioned and Normodyne, which is only approved for hypertension. There is a significant side effect profile associated with the latter product. In the B1 selective products, it was noted that all 5 are available generically, many containing a diuretic in combination. Varying indications were noted. MERIT and other studies have been noted in presentations.

B1 and B2 selective agents include such products as Corgard. Sotolol was noted as interesting. A reference was made to Betapace & Betapace AF, which are the same product, varying only in packaging which promotes the product use in A-fib. The beta blockers were not used for CHF until recently; now low-dose therapy is used with success.

Mr. Szalwinski recommended the class be included in the PDL eligible list.

Mr. Oley requested utilization data on drugs within categories. Mr. Finnerty assured the Committee this material would be forthcoming.

Dr. Axelrod asked if the Committee was ready to vote. Motion and second (Cantrell/Johnson) moved the question. The vote was unanimous to include this therapeutic class in the PDL. No vote was submitted via phone.

Dr. Axelrod noted there would be no confidential meeting following the open session. Since DMAS will not be involved in the pooled rebate program there is no need for a confidential meeting at this time. He reminded those present that contract proposals are due by October 3.

The next meeting is scheduled for October 15 at 1:00 PM in the DMAS Board Room. The primary focus of the meeting will be consideration of the contract proposals. There will be no consideration of additional drug classes for the initial PDL implementation. The public meeting will be short, moving quickly to the confidential meeting. Dr. Axelrod encouraged Committee members to make every effort to attend in person, so that a quorum can be had.

Dr. Axelrod thanked staff for the comprehensive background materials. He made special note of the glossary of drug study acronyms. He stated the information presented was pertinent and timely.

Chairman Axelrod adjourned the meeting at 12:05 P.M.